CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074744

Trade Name : SELEGILINE HCL TABLETS 5MG

Generic Name: Selegiline HCl Tablets 5mg

Sponsor : Lemmon Company

Approval Date: January 27, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074744

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074744

APPROVAL LETTER

ANDA 74-744

JAN 27 1997

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Madam:

This is in reference to your abbreviated new drug application dated September 8, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Selegiline Hydrochloride Tablets USP, 5 mg.

Reference is also made to your amendments dated December 10, 1996, and January 10, and January 23, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Selegiline Hydrochloride Tablets USP, 5 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

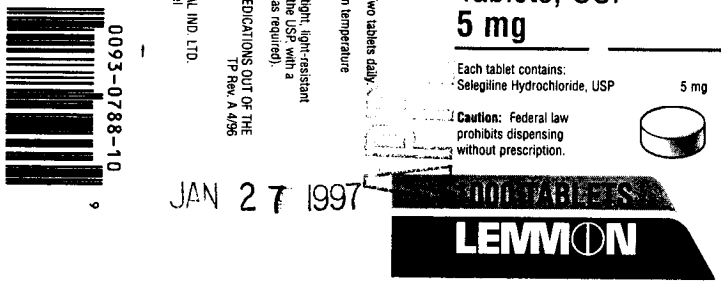
D. L. Sporn

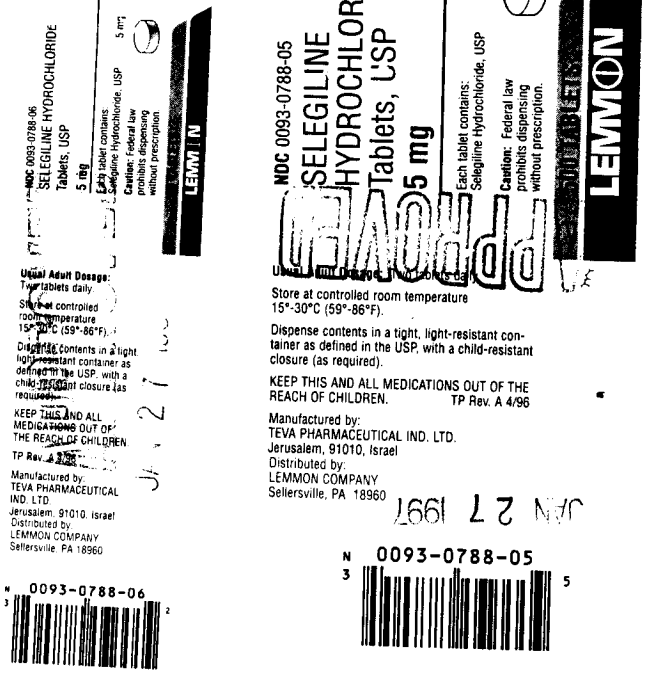
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074744

FINAL PRINTED LABELING


NDC 0093-0788-10
SELEGILINE HYDROCHLORIDE
Tablets, USP
5 mg
Each tablet contains:
Selegiline Hydrochloride, USP 5 mg
Caution: Federal law prohibits dispensing without prescription.
Usual Adult Dosage: Two tablets daily.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
TP Rev. A 4/96
Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Distributed by:
LEMMON COMPANY
Sellersville, PA 18960
N 3 0093-0788-10 9
JAN 27 1997
100 TABLETS
LEMMON


NDC 0093-0788-06
SELEGILINE HYDROCHLORIDE
Tablets, USP
5 mg
Each tablet contains:
Selegiline Hydrochloride, USP 5 mg
Caution: Federal law prohibits dispensing without prescription
LEMMON
Usual Adult Dosage:
Two tablets daily.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN
TP Rev. A 4/96
Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Distributed by:
LEMMON COMPANY
Sellersville, PA 18960
N 3 0093-0788-06 2
NDC 0093-0788-05
SELEGILINE HYDROCHLORIDE
Tablets, USP
5 mg
Each tablet contains:
Selegiline Hydrochloride, USP 5 mg
Caution: Federal law prohibits dispensing without prescription.
100 TABLETS
LEMMON
Store at controlled room temperature 15°-30°C (59°-86°F).
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Sellersville, PA 18960
JAN 27 1997
N 3 0093-0788-05 5

R 3 56 8 12

0788 **SELEGILINE HYDROCHLORIDE TABLETS, USP**

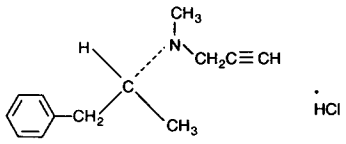
JAN 27 1997

APPROVED

DESCRIPTION

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as L-deprenyl.

The chemical name is: (R)-(-)-N,2-dimethyl-N-2-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol. The structural formula is as follows:



$C_{13}H_{18}ClN$ M.W. 223.75

Each tablet, for oral administration, contains 5 mg of selegiline hydrochloride. In addition, each tablet contains the following inactive ingredients: citric acid, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a "suicide" substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because selegiline has greater affinity for type B than for type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a "hypertensive crisis," the so-called "cheese reaction." (If large amounts of certain exogenous amines gain access to the systemic circulation - e.g., from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc. - they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 mg a day can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. However, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). The pathophysiology of the "cheese reaction" is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons.

However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g. 10 mg/day). **In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)**

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

Rationale for the Use of a Selective Monoamine Oxidase Type B Inhibitor in Parkinson's Disease

Many of the prominent symptoms of Parkinson's disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's disease, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa).

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (i.e., there is "wearing off"), and is often accompanied by side effects (e.g., dyskinesia, akinesias, on-off phenomena, freezing, etc.)

This deteriorating response is currently interpreted as a manifestation of the inability of the ever decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabolism of dopamine, it would increase the net amount of dopamine available (i.e., it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive selegiline is unknown.

Selegiline's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement and toxic delirium.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination - ADME)

Only preliminary information about the details of the pharmacokinetics of selegiline and its metabolites is available.

Data obtained in a study of 12 healthy subjects that was intended to examine the effects of selegiline on the ADME of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to these subjects, serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Three metabolites, N-desmethyldeprenyl, the major metabolite (mean half-life 2.0 hours), amphetamine (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these 3 metabolites.

In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of selegiline hydrochloride for seven consecutive days. Under these conditions, the mean trough serum levels for amphetamine were 3.5 ng/mL and 8.0 ng/mL for methamphetamine; trough levels of N-desmethyldeprenyl were below the levels of detection.

The rate of MAO B regeneration following discontinuation of treatment has not been quantitated. It is this rate, dependent upon de novo protein synthesis, which seems likely to determine how fast normal MAO B activity can be restored.

INDICATIONS AND USAGE

Selegiline Hydrochloride Tablets are indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of "off" time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS

Selegiline hydrochloride is contraindicated in patients with a known hypersensitivity to this drug.

Selegiline is contraindicated for use with meperidine. This contraindication is often extended to other opioids. (See Drug

Selegiline's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa therapy. Whether it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement and toxic delirium.

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CONTRAINDICATIONS

Selegiline hydrochloride is contraindicated in patients with a known hypersensitivity to this drug.

Selegiline is contraindicated for use with meperidine. This contraindication is often extended to other opioids. (See Drug Interactions.)

WARNINGS

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (Phenelzine, Tranylcypromine). A similar reaction has been reported for a patient on amitriptyline and selegiline. Another patient receiving protriptyline and selegiline developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after selegiline was added. Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving selegiline and various tricyclic antidepressants.

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride and non-selective MAOIs. Similar signs have been reported in some patients on the combination of selegiline (10 mg a day) and selective serotonin reuptake inhibitors including fluoxetine, sertraline and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of selegiline and tricyclic antidepressants as well as selegiline and selective serotonin reuptake inhibitors. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with a tricyclic antidepressant or selective serotonin reuptake inhibitors. Because of the long half lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with selegiline.

PRECAUTIONS:

General

Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reaction with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of selegiline therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the "cheese reaction" provided. While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests

No specific laboratory tests are deemed essential for the management of patients on selegiline. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions

The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine. Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination. (See CONTRAINDICATIONS.) Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and selegiline and selective serotonin reuptake inhibitors and selegiline. (See WARNINGS for details.) One case of hypertensive crisis has been reported in a patient taking the recommended doses of selegiline and a sympathomimetic medication (ephedrine).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Assessment of the carcinogenic potential of selegiline in mice and rats is ongoing.

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in *Salmonella typhimurium* and an *in vivo* chromosomal aberration assay. While these studies provide some reassurance that selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations. No definitive *in vitro* chromosomal aberration or *in vitro* mammalian gene mutation assays have been performed.

The effect of selegiline on fertility has not been adequately assessed.

Pregnancy, Teratogenic Effects, *Pregnancy Category C.* No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12 and 35 times the human therapeutic dose on a mg/m^2 basis. No teratogenic effects were observed in a study of embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m^2 basis; however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat study, there was a decrease in fetal body weight at the highest dose tested. In the rabbit study, increases in total resorptions and % post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- and postnatal development study in Sprague-Dawley rats (oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m^2 basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated offspring was not assessed.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether selegiline is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use
The effects of selegiline hydrochloride in pediatric patients have not been evaluated.

ADVERSE REACTIONS

Introduction
The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have been also reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with selegiline obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N=49	placebo N=50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry Mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg Pain	1	0
Low Back Pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

CENTRAL NERVOUS SYSTEM
Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

AUTONOMIC NERVOUS SYSTEM
dry mouth, blurred vision, sexual dysfunction.

CARDIOVASCULAR
orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

GASTROINTESTINAL
nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

GENITOURINARY/GYNECOLOGIC/ENDOCRINE
slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*; urinary frequency.

SKIN AND APPENDAGES
increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

MISCELLANEOUS
asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS
The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of selegiline hydrochloride.

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

* indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE

Selegiline
No specific information is available about clinically significant overdoses with selegiline hydrochloride. However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors (e.g., tranylcypromine, isocarboxazid, and phenelzine).

Overdose with Non-Selective MAO Inhibition
NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion, of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of the

GENITOURINARY/GYNECOLOGIC/ENDOCRINE
slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

SKIN AND APPENDAGES
increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

MISCELLANEOUS
asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS
The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of selegiline hydrochloride.

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

* indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE
Selegiline
No specific information is available about clinically significant overdoses with selegiline hydrochloride. However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors (e.g., tranylcypromine, isocarboxazid, and phenelzine).

Overdose with Non-Selective MAO Inhibition
NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion, of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions for Overdose
NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION
Selegiline Hydrochloride Tablets are intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of selegiline hydrochloride is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

HOW SUPPLIED
Selegiline Hydrochloride Tablets, USP 5 mg are white to off-white, unscored, round, flat, beveled tablets debossed "93" on one side and "788" on the other side. Available in bottles of 60, 500 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

For:
LEMMON COMPANY
Sellersville, PA 18960

Rev. C 6/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074744

CHEMISTRY REVIEW(S)

ANDA No. 74-744, Selegiline Hydrochloride Tablets USP, 5 mg

ADDENDUM TO CHEMISTRY REVIEW NO. 3

Per Ms. F. Fang's request, the firm was requested to specify the facility where the stability studies pertaining to the subject ANDA were/will be performed. The firm responded that TEVA Pharmaceutical located at Hashikma Street, Industrial Area, P.O. Box 353, Kfar Sava, Israel, conducted the stability studies for the bio batch and will perform post-approval stability studies in accordance with ANDA specifications.

Recommend approval of the subject application.

Edwin Ramos, Chemist Reviewer
01/12/97

1/12/97

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-744

3. NAME AND ADDRESS OF APPLICANT
Lemmon Company
Attention: Ms. Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. BASIS OF SUBMISSION
The new indication exclusivity for selegiline expired on June 5, 1994. The orphan drug exclusivity for selegiline hydrochloride tablets expired on June 5, 1996.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Eldepryl

7. NONPROPRIETARY NAME
Selegiline Hydrochloride

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
September 8, 1995-- Original Submission
October 30, 1995-- Refuse to file letter
November 9, 1995-- Amendment
December 8, 1995-- Acknowledgement--Acceptable for filing
February 23, 1996- Labeling review
April 17, 1996-- Deficiency letter
July 19, 1996-- Amendment
October 24, 1996-- Deficiency letter
December 10, 1996-- Amendment

10. PHARMACOLOGICAL CATEGORY
Antiparkinson Agent

11. Rx or OTC
Rx

12. RELATED Drug Master Files
10235--Assia-nds
5798--Econopak
885--Quantum
8394--Ampacet
2229--Owens Illinois
4162--U.S. Can
7325--Huntsman
1378--Tekni-Plex
8260--Anchor Hocking
2880--United Desiccants
4164--American White Cross

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg

15. CHEMICAL NAME AND STRUCTURE
(R)-(-)-N,2-dimethyl-N-2-propynylphenethylamine hydrochloride

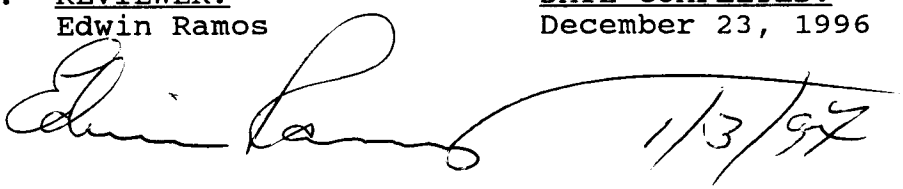
16. RECORDS AND REPORTS
N/A

17. COMMENTS
None

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
December 23, 1996



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074744

BIOEQUIVALENCE REVIEW(S)

JUL 17 1996

Selegiline Hydrochloride
5 mg Tablets
ANDA # 74-744
Reviewer: Man M. Kochhar

Lemmon Company
Sellersville, PA
Submission Date:
September 8, 1995

Review of Bioequivalence Study and Dissolution

(Fasting and Non-fasting)

OBJECTIVE:

The objective of this study was to determine the bioequivalence of the 5 mg generic Selegiline tablet with the marketed 5 mg Eldepryl tablets by Somerset Pharmaceuticals in healthy subjects under fasting and non-fasting conditions. The effects of the food on the pharmacokinetics of selegiline were also evaluated.

INTRODUCTION:

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly known as l-deprenyl. It is white crystalline powder, freely soluble in water, chloroform and methanol.

Selegiline hydrochloride tablets are indicated as an adjunct in the management of parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. Selegiline is an irreversible inhibitor of monoamine oxidase (MAO), Type B. The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood.

Following the oral administration of a single dose of 10 mg of selegiline hydrochloride, serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Three metabolites, N-desmethylselegiline, the major metabolite (mean half-life 2.0 hours), amphetamine (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these 3 metabolites.

The recommended regimen for the administration of selegiline hydrochloride is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch.

IN-VIVO STUDY:

The objective of this study was to compare the bioavailability of Lemmon and Somerset (Eldepryl) 5 mg tablets under fasting and non-fasting conditions.

The bioequivalence study was conducted by Phoenix International, Montreal, Canada, under the supervision of Jacques Y. Gareau, M.D., and Richard Lalonde, Pharm D.

STUDY DESIGN:

1. The fasting study was designed as a randomized, single dose (2 x 5 mg tablet), two-way crossover bioequivalence study in 32 healthy volunteers (protocol # 941527).

2. The non-fasting study was designed as a randomized, three-way crossover, single dose (2 x 5 mg tablet) bioequivalence study in 18 healthy volunteers (protocol # 941528).

Subjects:

The study employed thirty-two (32) subjects for fasting study and eighteen (18) subjects for non-fasting study between the ages of 18-45, whose weight did not deviate by more than ±15% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for at least 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing until after completion of the study. Each subject signed a written informed consent.

The subjects remained in the clinic from 12 hours before dosing until after the 36-hour blood draw.

Methods:

The product and dosage employed in this study were as follows:

FASTING:

Treatment A. Test: 2 x 5 mg Selegiline Hydrochloride tablet, lot # K-18339 with 240 mL of water (Fasting).

Batch size:150,000 tablets,
Content Uniformity: 99.2% Date Manufactured: 5-94
Potency: 97.8%

Treatment B. Reference: 2 x 5 mg Eldepryl (Somerset), lot # 3Z022M with 240 mL of water (Fasting).

Expiry Date: 6/95. Content Uniformity: 97.2%
Potency: 97.3%

NON-FASTING:

Treatment C. Test: 2 x 5 mg Selegiline hydrochloride tablet, lot # K-18339 with 240 mL of water (fasting).

Treatment D. Test: 2 x 5 mg selegiline hydrochloride tablet, lot # K-18339 with 240 mL of water (Non-fasting).

Treatment E. Reference: 2 x 5 mg Eldepryl tablet (Somerset), lot # 3Z022M with 240 mL of water (Non-fasting).

In treatments # A, B and C subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water will not be permitted for 2 hours before and 4 hours after dosing but will be allowed at all other times.

In a non-fasting treatments # D and E subjects fasted overnight until 30 minutes prior to their schedule dosing times, when they were given a standard breakfast.

Two times 7 mL (2 x 7 mL) of venous blood were drawn into a Vacutainers with EDTA at 0 and (1 x 7 mL) at 0.167, 0.33, 0.50, 0.67, 0.833, 1, 1.167, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours. The plasma was separated and promptly frozen for analysis.

Plasma selegiline and desmethylselegiline levels were determined for samples drawn pre-dose and at following times post-dose: 0.167, 0.33, 0.5, 0.67, 0.833, 1, 1.167, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, and 18 hours.

Plasma amphetamine and methamphetamine levels were determined for samples drawn pre-dose and at the following times post-dose: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72.

WASHOUT PERIOD: 14 days

ANALYTICAL METHODOLOGY: Selegiline, desmethylselegiline, amphetamine and methamphetamine in plasma were measured by a specific LS/MS/MS assay method developed by the company.

ASSAY VALIDATION:

Selegiline

1. Linearity: 50 to 10005.5 pg/mL.

2. Sensitivity: 50 pg/mL. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma samples from the subjects in the study indicated no interference with drug or the internal standard.

4. Accuracy & Precision:

Between-Batch (N=6)	Concentration of Selegiline (pg/mL)			
Actual (pg/mL)	50.1	150.2	4005.6	8011.1
Observed (pg/mL)	47.13	144.55	3964.96	7778.25
Accuracy %	94.1	96.2	99.0	97.1
CV %	13.7	5.0	2.3	3.4
Within-Batch (N=10)				
Actual (pg/mL)	50.1	150.2	4005.6	8011.1
Observed (pg/mL)	53.74	147.87	3844.13	7561.65
Accuracy %	107.3	98.4	96.00	94.4
CV%	12.2	6.6	3.9	4.8

5. The assay was validated by analyzing four standard curve sets with 3 sets of high (8011.1 pg/mL), medium (4005.6 pg/mL) and low (150.2 pg/mL and 50.1 pg/mL) QC samples. The assay was documented to be reproducible. For standards, the between-batch precision showed mean CVs less than 14% and within-batch accuracy mean CVs were less than 12.2%.

6. The percent recovery was determined by measuring the absolute peak height of selegiline and internal standard from a plasma sample. The mean recovery was 84% for 150.2 pg/mL; 77.5% for 4005.6 pg/mL and 76.5% for 8011.1 pg/mL.

7. The stability studies showed that selegiline is stable at room temperature for at least 8 hours; at least 321 days at -20°C. The stability of selegiline was also determined in triplicate at low, and high concentrations (150.2 and 8011.1 pg/mL) during three freeze-thaw cycles. The ratio of means (stability vs comparison was 103% for low and 100.4% for high concentrations.

   It was concluded that freezing and thawing spiked plasma samples over three cycles does not alter the integrity of selegiline.

Desmethylselegiline

1. Linearity: 199.8 to 19982.8 pg/mL

2. Sensitivity: 199.8 pg/mL. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma samples from the subjects in the study indicated no interference with desmethylselegiline or the internal standard.

4. Accuracy & Precision:

Between-Batch (N=6)	Conc. of desmethylselegiline (pg/ml)			
Actual (pg/mL)	200.0	600.0	7999.7	15999.5
Observed (pg/mL)	189.04	563.69	7787.54	15845.62
Accuracy %	94.5	93.9	97.3	99.0
CV %	15.2	2.8	6.0	3.4
Within-Batch (N=10)				
Actual (pg/mL)	200.0	600.0	7999.7	15999.5
Observed (pg/mL)	180.69	577.86	7794.92	15278.66
Accuracy %	90.3	96.3	97.4	95.5
CV%	7.2	8.1	5.5	3.5

5. The assay was validated by analyzing four standard curve sets with 3 sets of high (15999.5 pg/mL), medium (7999.7 pg/mL) and low (200 pg/mL and 600 pg/mL) QC samples. The assay was documented to be reproducible. For standards, the between-batch precision showed mean CVs less than 15% and within-batch accuracy mean CVs were less than 8.1%.

6. The percent recovery was determined by measuring the absolute peak height of desmethylselegiline and internal standard from a plasma sample. The mean recovery was 72.6% for 600 pg/mL; 82.7% for 7999.7 pg/mL and 79.0% for 15999.5 ng/mL.

7. The stability studies showed that desmethylselegiline is stable at room temperature for at least 7.8 hours; at least 321 days at -20°C. The stability of desmethylselegiline was also determined in triplicate at low, and high concentrations (20 and 255 ng/mL) during three freeze-thaw cycles. The ratios of means (stability vs comparison) were 100.5 for low concentration (600 pg/mL) and 100% for high concentration (15999.5 pg/mL).

   It was concluded that freezing and thawing spiked plasma samples over three cycles does not alter the integrity of desmethylselegiline.

Amphetamine

1. Linearity: 0.2 to 20. ng/mL.

2. Sensitivity: 0.2 ng/mL. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma samples from the subjects in the study indicated no interference with drug or the internal standard.

4. Accuracy & Precision:

Between-Batch (N=6)	Concentration of Amphetamine (ng/mL)			
Actual (ng/mL)	0.200	0.600	6.01	16.003
Observed (ng/mL)	0.1830	0.5660	5.7367	15.9481
Accuracy %	91.3	96.2	99.0	97.1
CV %	15.3	6.2	4.8	5.7

Within-Batch (N=10)				
Actual (ng/mL)	0.200	0.600	6.001	16.003
Observed (ng/mL)	0.2153	0.5835	5.6225	15.1811
Accuracy %	107.7	97.3	93.7	94.9
CV%	5.7	6.9	4.5	7.3

5. The assay was validated by analyzing four standard curve sets with 3 sets of high (16.003 ng/mL), medium (6.01 ng/mL) and low (0.200 ng/mL and 0.600 ng/mL) QC samples. The assay was documented to be reproducible. For standards, the between-batch precision showed mean CVs less than 15% and within-batch accuracy mean CVs were less than 7.3%.

6. The percent recovery was determined by measuring the absolute peak height of amphetamine and internal standard from a plasma sample. The mean recovery was 70.1% for .600 ng/mL; 74.7% for 6.001 ng/mL and 72.9% for 16.003 ng/mL.

7. The stability studies showed that amphetamine is stable at room temperature for at least 3.8 hours; at least 50 days at -20°C. The stability of amphetamine was also determined in triplicate at low, and high concentrations (0.600 and 16.003 ng/mL) during three freeze-thaw cycles. The ratio of means (stability vs comparison was 101.4% for low and 98.6% for high concentrations.

   It was concluded that freezing and thawing spiked plasma samples over three cycles does not alter the integrity of amphetamine.

Methamphetamine

1. Linearity: 0.4 to 20.0 ng/mL

2. Sensitivity: 0.4 ng/mL. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma samples from the subjects in the study indicated no interference with methamphetamine or the internal standard.

4. Accuracy & Precision:

Between-Batch (N=6)	Conc. of methamphetamine (ng/ml)			
Actual (ng/mL)	0.399	1.198	5.991	13.979
Observed (ng/mL)	0.4203	1.1130	5.7468	13.5088
Accuracy %	105.3	92.9	95.9	96.6
CV %	6.4	4.2	4.1	4.4

Within-Batch (N=10)				
Actual (ng/mL)	0.399	1.198	5.991	13.979
Observed (ng/mL)	0.4347	1.1447	5.6928	12.7907
Accuracy %	108.9	95.6	95.0	91.5
CV%	7.2	6.2	5.2	6.7

5. The assay was validated by analyzing four standard curve sets with 3 sets of high (13.979 ng/mL), medium (5.991 ng/mL) and low (1.198 ng/mL and 0.399 ng/mL) QC samples. The assay was documented to be reproducible. For standards, the between-batch precision showed mean CVs less than 6.4% and within-batch accuracy mean CVs were less than 7.2%.

6. The percent recovery was determined by measuring the absolute peak height of methamphetamine and internal standard from a plasma sample. The mean recovery was 75.2% for 1.198 ng/mL; 82.1% for 5.991 ng/mL and 78.7% for 13.979 ng/mL.

7. The stability studies showed that methamphetamine is stable at room temperature for at least 3.4 hours; at least 50 days at -20°C. The stability of methamphetamine was also determined in triplicate at low, and high concentrations (1.198 and 13.979 ng/mL) during three freeze-thaw cycles. The ratios of means (stability vs comparison) were 109.9 for low concentration (1.198 ng/mL) and 98.3% for high concentration (13.979 ng/mL).

   It was concluded that freezing and thawing spiked plasma samples over three cycles does not alter the integrity of methamphetamine.

DATA ANALYSIS:

Statistical significance of differences due to treatments, study days, dosing sequence, subjects within sequence, in plasma selegiline, desmethylselegiline, amphetamine and methamphetamine concentrations at each sampling time and its pharmacokinetic parameters were determined by analysis of variance (ANOVA) using Statistical Analysis Systems (SAS) general linear model (GLM) procedure. 90% confidence intervals (two one-sided t-test) were calculated for pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

FASTING STUDY

Treatment A & B

Of the thirty-two (32) subjects in the study, 2 did not complete the crossover. Subject # 10 and 31 were withdrawn from the study prior to period 2 dosing due to medical events judged to be related to study drugs or procedures. The plasma samples from the 30 subjects were assayed for selegiline, desmethylselegiline, amphetamine and methamphetamine as per the protocol.

Selegiline

The results of the study comparing the bioavailability of selegiline (test) and Eldepryl (reference) products are given in Table 1 and 2. The mean plasma selegiline concentrations for test and reference treatments are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Selegiline (N=30)

Time (hours)	Lemmon's Selegiline Lot # K-18339 pg/mL (%CV)	Somerset's Eldepryl Lot # 3Z022M pg/mL (%CV)	T/R
0.00	0.0	0.0	0.00
0.167	12.4 (291)	13.2 (250)	0.94
0.33	242.3 (226)	215.4 (185)	1.12
0.5	813.7 (160)	667.8 (126)	1.22
0.667	748.0 (134)	707.4 (142)	1.05
0.833	636.2 (140)	587.5 (152)	1.08
1.0	425.0 (140)	356.9 (127)	1.19
1.167	326.9 (151)	281.6 (130)	1.16

1.33	227.0 (128)	236.6 (128)	0.96
1.5	176.2 (127)	170.5 (117)	1.03
1.75	125.8 (109)	117.2 (110)	1.07
2.0	86.8 (131)	92.6 (118)	0.94
2.5	54.5 (158)	66.7 (142)	0.82
3.0	43.0 (177)	42.8 (167)	1.00
4.0	24.6 (192)	19.1 (221)	1.29
5.0	7.9 (311)	11.4 (264)	0.69
6.0	3.7 (548)	8.6 (262)	0.43
8.0	2.1 (548)	6.6 (313)	0.32
12.0	1.9 (548)	0.0 (---)	0.00
16.0	0.0 (---)	0.0 (---)	0.00

TABLE 2

A Summary of Selegiline Pharmacokinetic Parameters for 30 Subjects (%CV)

Parameters	**Lemmon**[1s] Mean (CV%)	Somerset's[2] Mean (CV%)	T/R	90% Confidence **Interval**
AUC_{0-16} pg.hr/mL	763.4 (131)	702.3 (131)	1.09	73; 144
AUC_{inf} pg.hr/mL	918.9 (116)	869.8 (113)	1.06	76; 159
C_{max} pg/mL	1086.4 (133)	910.7 (122)	1.19	83; 155
T_{max} hours	0.666 (28)	0.660 (30)	1.00	
K_{el} 1/hr	1.1293(57)	1.1501 (63)	0.98	
$t_{1/2}$ hours	0.9975(80)	0.9386 (70)	1.06	
Ln AUC_{0-16} pg.hr/mL	409.5 (163)	425.2 (124)	0.96	80; 115
Ln AUC_{inf} pg.hr/mL	589.2 (111)	591.8 (98)	0.99	91; 124
Ln C_{max} pg/mL	574.5 (163)	576.1 (120)	0.99	80; 124

1. AUCinf, Kel and t1/2 could not be estimated for some subject For log-transformed parameters, the antilog of the mean is reported.

Desmethylselegiline

The results of plasma concentration and pharmacokinetic parameters for desmethylselegiline in plasma are given in Table 3 and 4 and Figure 2.

TABLE 3

Mean Plasma Concentration of Desmethylselegiline (N=30)

Time (hours)	Lemmon's Selegiline Lot # K-18339 pg/mL (%CV)	Somerset's Eldepryl Lot # 3Z022M pg/mL (%CV)	T/R
0.00	0.0	0.0	0.00
0.167	37.8 (326)	99.4 (192)	0.38
0.33	2194.6 (134)	4242.4 (129)	0.52
0.5	8294.2 (76)	7984.4 (60)	1.04
0.67	11716.9 (45)	11519.2 (40)	1.02
0.833	13223.0 (34)	12777.4 (36)	1.03
1.0	12064.1 (33)	11535.2 (29)	1.04
1.167	11176.1 (36)	10549.6 (30)	1.06
1.33	9727.4 (37)	9372.5 (30)	1.04
1.5	8405.0 (38)	8331.8 (30)	1.01
1.75	7030.3 (36)	6856.4 (31)	1.02
2.0	5873.7 (38)	5813.3 (33)	1.01
2.5	4570.1 (44)	4488.3 (38)	1.02
3.0	3571.5 (45)	3473.5 (42)	1.03
4.0	2304.0 (45)	2236.1 (46)	1.03
5.0	1475.0 (44)	1453.3 (46)	1.01
6.0	1161.5 (45)	1132.0 (45)	1.02
8.0	727.5 (48)	708.4 (52)	1.03
12.0	343.9 (68)	353.7 (65)	0.97
16.0	175.7 (100)	153.2 (111)	1.15

TABLE 4

A Summary of Desmethylselegiline Pharmacokinetic Parameters for 30 Subjects (%CV)

Parameters	Lemmon's Mean (CV%)	Somerset's Mean (CV%)	T/R	90% Confidence Interval
AUC_{0-16} pg.hr/mL	31271.1 (38)	30433.8 (36)	1.03	97; 108
AUC_{inf} pg.hr/mL	32886.9 (38)	31988.7 (36)	1.03	98; 108
C_{max} pg/mL	14457.6 (34)	13807.7 (32)	1.05	95; 114
T_{max} hours	0.846 (23)	0.815 (23)	1.04	
K_{el} 1/hr	0.2118 (37)	0.2085 (30)	1.01	
$t_{1/2}$ hours	3.632 (29)	3.582 (26)	1.01	
Ln AUC_{0-16} pg.hr/mL	29083.3 (41)	28617.9 (37)	1.02	96; 107
Ln AUC_{inf} pg.hr/mL	30615.6 (40)	30128.1 (36)	1.02	96; 107
Ln C_{max} pg/mL	13652.5 (36)	13199.5 (31)	1.03	97; 112

Amphetamine

The results of plasma concentration and pharmacokinetic parameters for amphetamine in plasma are given in Table 5 and 6 and Figure 3.

TABLE 5

Mean Plasma Concentration of Amphetamine (N=30)

Time (hours)	Lemmon's Selegiline Lot # K-18339 ng/mL (%CV)	Somerset's Eldepryl Lot # 3Z022M ng/mL (%CV)	T/R
0.00	0.0 (---)	0.00 (---)	0.00
0.50	0.36 (130)	0.31 (116)	1.16

1.0	1.69 (43)	1.70 (49)	0.99
2.0	2.70 (22)	2.78 (20)	0.97
3.0	2.98 (22)	2.93 (21)	1.01
4.0	2.95 (16)	3.05 (20)	0.97
6.0	3.36 (18)	3.35 (16)	1.00
8.0	3.52 (19)	3.45 (16)	1.02
12.0	3.12 (21)	3.17 (21)	0.98
16.0	2.55 (21)	2.54 (21)	1.00
24.0	1.72 (26)	1.74 (23)	0.99
36.0	1.18 (35)	1.18 (32)	1.00
48.0	0.70 (46)	0.74 (49)	0.95
72.0	0.27 (118)	0.24 (112)	1.12

TABLE 6

A Summary of Amphetamine Pharmacokinetic Parameters for 30 Subjects (%CV)

Parameters	**Lemmon's** Mean (CV%)	Somerset's Mean (CV%)	T/R	90% Confidence **Interval**
AUC_{0-72} ng.hr/mL	102.1 (24)	102.3 (21)	1.00	94; 106
AUC_{inf} ng.hr/mL	111.1 (25)	114.7 (27)	0.97	95; 105
C_{max} ng/mL	3.66(19)	3.65 (18)	1.00	95; 105
T_{max} hours	6.83 (38)	7.67 (41)	0.89	
K_{el} 1/hr	0.0421 (24)	0.0410(28)	1.02	
$t_{1/2}$ hours	17.30 (22)	18.44 (35)	0.94	
Ln AUC_{0-72} ng.hr/mL	99.29 (25)	100.20(21)	0.99	94; 105
Ln AUC_{inf} ng.hr/mL	107.75 (26)	111.42(24)	0.97	94; 104
Ln C_{max} ng/mL	3.60 (19)	3.59(17)	1.00	96; 105

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Methamphetamine

The results of plasma concentration and pharmacokinetic parameters for methamphetamine in plasma are given in Table 7 and 8 and Figure 4.

TABLE 7

Mean Plasma Concentration of Methamphetamine (N=30)

Time (hours)	Lemmon's Selegiline Lot # K-18339 pg/mL (%CV)	Somerset's Eldepryl Lot # 3Z002M pg/mL (%CV)	T/R
0.00	0.0	0.21 (548)	0.00
0.50	2.15 (147)	1.95 (96)	1.10
1.00	8.06 (38)	8.04 (42)	1.00
2.00	10.69 (17)	11.13 (18)	0.96
3.00	11.03 (15)	11.15 (17)	0.99
4.00	10.60 (15)	10.98 (16)	0.96
6.00	11.05 (19)	11.08 (15)	0.99
8.00	10.86 (21)	10.96 (19)	0.99
12.00	8.61 (25)	9.05 (23)	0.95
16.00	6.64 (25)	6.96 (30)	0.95
24.00	4.21 (36)	4.38 (35)	0.96
36.00	2.55 (47)	2.63 (46)	0.97
48.00	1.39 (56)	1.52 (65)	0.91
72.00	0.39 (104)	0.43 (143)	0.91

TABLE 8

A Summary of Methamphetamine Pharmacokinetic Parameters for 30 Subjects (%CV)

Parameters	Lemmon's Mean (CV%)	Somerset's Mean (CV%)	T/R	90% Confidence Interval
AUC_{0-72} ng.hr/mL	271.3 (28)	280.3 (29)	0.97	89; 104
AUC_{inf} ng.hr/mL	288.6 (29)	303.8 (31)	0.95	88; 102
C_{max} ng/mL	12.1 (18)	12.2 (19)	0.99	95; 103
T_{max} hours	4.57 (50)	4.37 (54)	1.04	

K_{el} 1/hr	0.0497 (24)	0.0491 (25)	1.01	
$t_{1/2}$ hours	14.67 (22)	15.16 (30)	0.97	
Ln AUC_{0-72} ng.hr/mL	261.88 (27)	271.01 (26)	0.97	90; 103
Ln AUC_{inf} ng.hr/mL	278.54 (27)	292.41 (27)	0.95	89; 101
Ln C_{max} ng/mL	11.95 (17)	12.06 (18)	0.99	95; 103

Selegiline

The ratios of arithmetic means (with 90% confidence intervals) for the AUCo-t, AUCinf and Cmax were 1.08 (73 to 144), 1.06 (76 to 159) and 1.19 (83 to 155), respectively. The results for log transformed were as follows: The 90% confidence intervals for ln AUCo-t., ln AUCinf and ln Cmax were 80 to 115, 91 to 124 and 80 to 124 respectively. The mean Tmax for the Lemmon product was 0.666 hours, compared with 0.660 hours for the Somerset product (reference). The K_{el} and $t_{1/2}$ values differ by 1.81% and 6.28% respectively.

The selegiline concentration/time profiles of the two products showed significant differences at 5, 6, and 8 hours after dosing.

Desmethylselegiline

The ratios of means (with 90% confidence intervals) for the ln-transformed parameters AUCo-12, AUCinf, and Cmax were 1.02 (96 to 107), 1.02 (96 to 107) and 1.03 (97 to 112), respectively. Similar results were obtained for the untransformed parameters. The mean Tmax for the test drug was 0.846 hours, compared with 0.815 hours for the reference drug. The Kel and t1/2 values differ by 1.58% and 1.41% respectively.

The desmethylselegiline concentration/time profiles of the two products showed significant differences at 0.167 and 0.33 hours after dosing.

Amphetamine

The ratios of means (with 90% confidence intervals) for the ln-transformed parameters AUCo-t, AUCinf, and Cmax were 0.99 (94 to 105), 0.97 (94 to 104) and 1.00 (96 to 105) respectively. The mean Tmax for test drug was 6.83 hours, compared with 7.67 hours for the

reference drug.

The amphetamine concentration/time profile of two products showed no significant difference at any time point.

Methamphetamine

The ratios of least-squares means (with 90% confidence intervals) for the ln-transformed parameters AUCo-t, AUCinf and Cmax were 0.97 (90 to 103), 0.95 (89 to 101) and 0.99 (95 to 103), respectively. The mean Tmax for the Lemmon product was 4.57 hours, compared with 4.37 hours for the Somerset product.

The methamphetamine concentration/time profile of two products showed no significant differences at any time point.

No serious adverse effects were experienced by any subject during the study.

NON-FASTING

Treatment # C, D & E

Among the 18 subjects enrolled in the study, one subject (#18) elected to withdraw from the study for personal reasons approximately 32 minutes prior to period 2 dosing. Thus, a total of 17 subjects completed the study. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of selegiline hydrochloride under fasting and test and reference non-fasting selegiline, desmethylselegiline, amphetamine and methamphetamine are given in Tables 9, 10, 11, 12, 13, 14, 15 and 16. The mean plasma selegiline, desmethylselegiline, amphetamine and methamphetamine concentrations are given in Figure 4, 5, 6, and 7.

Selegiline

TABLE 9

Mean Plasma Concentration of Selegiline (N=17)

Time Hours	Lemmon's Selegiline pg/mL (CV%)		Somerset's Eldapryl pg/mL (CV%)	T/R (D/E)
	FASTING Treat. C	NON-FASTING Treat. D	NON-FASTING Treat. E	
0.0	0.00 (---)	0.00 (---)	0.00 (---)	0.00
0.167	23.99 (165)	110.54 (180)	37.18 (172)	2.97
0.33	388.55 (138)	1474.94 (138)	1074.88 (164)	1.37

0.5	1898.01 (109)	2177.27 (128)	1755.67 (151)	1.24
0.67	2214.98 (89)	2216.39 (100)	2004.58 (120)	1.10
0.83	1542.97 (94)	1648.15 (84)	2001.92 (80)	0.82
1.0	1023.13 (77)	1609.66 (94)	1796.49 (64)	0.89
1.167	925.05 (100)	1380.29 (89)	1818.72 (71)	0.76
1.33	625.45 (91)	1421.71 (88)	1712.36 (72)	0.83
1.5	489.41 (104)	1132.22 (73)	1411.50 (84)	0.80
1.75	345.85 (110)	1012.12 (78)	1237.78 (91)	0.82
2.0	254.88 (109)	952.58 (94)	963.81 (101)	0.99
2.5	149.59 (97)	549.74 (105)	575.35 (127)	0.96
3.0	116.45 (108)	423.34 (96)	470.59 (151)	0.90
4.0	62.65 (114)	184.57 (97)	212.47 (131)	0.87
5.0	50.38 (124)	91.37 (126)	115.90 (112)	0.79
6.0	31.89 (137)	54.19 (150)	66.09 (128)	0.82
8.0	20.75 (200)	40.33 (188)	39.59 (139)	1.02
12.0	3.46 (412)	15.61 (231)	21.68 (170)	0.72
16.0	3.34 (400)	8.62 (285)	8.35 (290)	1.03
24.0	0.00 (---)	3.76 (412)	0.00 (---)	0.00

TABLE 10
A SUMMARY OF SELEGILINE PHARMACOKINETIC PARAMETERS FOR 17 SUBJECTS
Non-Fasting

Parameters	**Lemmon's Selegiline HCl Mean (CV%)**		**Somerset's Eldepryl Mean (CV%)**	**T/R (D/E)**
	Fasting Treat. C	**Non-Fasting Treat. D**	**Non-Fasting Treat. E**	
AUC_{0-24} pg.hr/mL	2087.9 (85)	3983.6 (87)	4231.5 (86)	0.94
AUC_{inf} pg.hr/mL	2107.9 (86)	4383.3 (82)	4726.2 (80)	0.93
C_{max} pg/mL	2582.8 (89)	3147.4 (83)	3001.2 (80)	1.05
T_{max} hours	0.637 (30)	1.043 (69)	0.910 (49)	1.14
$t_{1/2}$ hours	2.166 (67)	2.047 (109)	2.636 (86)	0.78
K_{el} 1/hr	0.4414 (54)	0.6006 (58)	0.4671 (68)	1.28

Ln AUC_{0-24} pg.hr/mL	1367.8 (136)	2679.8 (130)	2978.8 (119)	0.90
Ln AUC_{inf} pg.hr/mL	1459.4 (114)	3136.1 (111)	3636.4 (87)	0.86
Ln C_{max} pg/mL	1664.9 (137)	2016.9 (158)	2222.3 (110)	0.91

Desmethylselegiline

TABLE 11

Mean Plasma Concentration of Desmethylselegiline (N=17)

Time Hours	**Lemmon's Selegiline Tab pg/mL (CV%)**		**Somerset's Eldepryl Tab. pg/mL (CV%)**	**T/R (D/E)**
	FASTING Treat. C	**NON-FASTING Treat. D**	**NON-FASTING Treat. E**	
0.0	0.00 (---)	0.00 (---)	0.00 (---)	0.00
0.167	263.95 (292)	369.99 (214)	82.64 (227)	4.47
0.33	3063.19 (134)	3427.34 (128)	2810.32 (127)	1.22
0.5	11189.13 (57)	6912.62 (100)	6319.66 (98)	1.09
0.67	16281.26 (34)	9051.94 (78)	8561.22 (67)	1.06
0.83	16507.71 (33)	9016.71 (71)	10036.08 (49)	0.90
1.0	15406.94 (27)	10220.83 (61)	10736.74 (34)	0.95
1.167	14062.87 (27)	9838.29 (55)	11433.34 (32)	0.86
1.33	12364.91 (25)	10105.26 (49)	11399.32 (24)	0.89
1.5	11637.65 (27)	9485.68 (41)	11151.01 (24)	0.85
1.75	9175.96 (28)	9218.58 (38)	10372.58 (29)	0.89
2.0	8086.22 (29)	8652.53 (38)	9347.25 (24)	0.93
2.5	6133.89 (29)	8076.96 (28)	8127.41 (26)	0.99
3.0	4810.11 (29)	7156.24 (30)	7196.23 (33)	0.99
4.0	3280.18 (31)	4908.39 (31)	4973.19 (52)	0.99
5.0	2299.85 (35)	3149.20 (30)	3272.92 (46)	0.96
6.0	1733.06 (36)	2179.88 (37)	2247.91 (36)	0.97
8.0	1142.28 (40)	1398.54 (43)	1422.36 (33)	0.98
12.0	596.12 (84)	695.28 (46)	693.55 (35)	1.00
16.0	372.48 (60)	426.48 (58)	446.29 (39)	0.96
24.0	92.42 (165)	140.58 (132)	!26.12 (117)	1.11

TABLE 12

A SUMMARY OF DESMETHYLSELEGILINE PHARMACOKINETIC PARAMETERS
FOR 15 SUBJECTS
Non-Fasting

Parameters	Lemmon's Selegiline Mean (CV%)		Somerset's Eldepryl Mean (CV%)	T/R (D/E)
	Fasting Treatment C	Non-Fasting D	Non-Fasting E	
AUC_{0-24} pg.hr/mL	45098.5 (29)	47741.4 (35)	49265.9 (25)	0.97
AUC_{inf} pg.hr/mL	47199.4 (29)	50031.6 (34)	51337.2 (25)	0.97
C_{max} pg/mL	19084.7 (28)	13646.8 (33)	13930.9 (28)	0.98
T_{max} hours	0.852 (33)	1.362 (63)	1.381 (54)	0.99
$t_{1/2}$ hours	4.590 (21)	4.827 (18)	4.780 (17)	1.01
K_{el} 1/hr	0.161 (25)	0.157 (29)	0.156 (27)	1.00
Ln AUC_{0-24} pg.hr/mL	43287.6(30)	45134.8(36)	47919.7(24)	0.94
Ln AUC_{inf} pg.hr/mL	45349.2(55)	47317.6(36)	49973.9(24)	0.95
Ln C_{max} pg/mL	18407.5(28)	12869.7(38)	13411.5(29)	0.96

Amphetamine

TABLE 13

Mean Plasma Concentration of Amphetamine (N=17)

Time Hours	Lemmon's Selegiline Tab. ng/mL (CV%)		Somerset's Eldepryl Tab. ng/mL (CV%)	T/R (D/E)
	FASTING Treat. C	NON-FASTING Treat. D	NON-FASTING Treat. E	
0.0	0.00 (---)	0.00 (---)	0.00 (---)	0.00
0.5	0.54 (97)	0.64 (114)	0.41 (130)	1.56
1.0	1.97 (37)	1.63 (76)	1.54 (45)	1.06
2.0	2.69 (27)	2.48 (46)	2.61 (28)	0.95
3.0	2.79 (24)	2.99 (32)	3.05 (20)	0.98
4.0	2.81 (23)	3.16 (29)	3.24 (16)	0.97
6.0	2.97 (20)	3.22 (25)	3.39 (15)	0.95
8.0	3.23 (21)	3.14 (27)	3.30 (17)	0.95
12.0	2.97 (18)	2.79 (26)	3.00 (19)	0.93
16.0	2.53 (18)	2.30 (28)	2.47 (20)	0.93
24.0	1.69 (29)	1.54 (38)	1.62 (23)	0.95
36.0	1.13 (34)	0.96 (37)	1.15 (31)	0.83
48.0	0.60 (48)	0.55 (50)	0.58 (54)	0.95
72.0	0.10 (147)	0.13 (136)	0.12 (131)	1.08

TABLE 14

A SUMMARY OF AMPHETAMINE PHARMACOKINETIC PARAMETERS FOR 17 SUBJECTS
Non-Fasting

Parameters	Lemmon's Seleginine Tab. Mean (CV%)		Somerset's Eldepryl tab Mean (CV%)	T/R (D/E)
	Fasting Treat. C	Non-Fasting D	Non-Fasting E	
AUC_{0-72} ng.hr/mL	93.1 (23)	88.0 (30)	94.7 (21)	0.93
AUC_{inf} ng.hr/mL	101.9 (22)	95.9 (29)	103.3 (21)	0.93
C_{max} ng/mL	3.4 (20)	3.6 (25)	3.6 (15)	1.00

T_{max} hours	8.3 (40)	5.9 (64)	5.9 (40)	1.00
$t_{1/2}$ hours	15.3 (22)	15.3 (22)	15.7 (18)	0.97
K_{el} 1/hr	0.047 (20)	0.047 (19)	0.046 (18)	1.00
Ln AUC_{0-72} ng.hr/mL	85.9 (28)	85.9 (23)	82.3 (24)	1.04
Ln AUC_{inf} ng.hr/mL	101.1 (30)	96.3 (21)	92.3 (26)	1.04
Ln C_{max} ng/mL	3.3 (14)	3.3 (14)	3.3 (12)	1.00

Methamphetamine

TABLE 15

Mean Plasma Concentration of Methamphetamine (N=17)

Time Hours	Lemmon's Selegiline Tab. ng/mL (CV%)		Somerset's Eldepryl Tab. ng/mL (CV%)	T/R (D/E)
	FASTING Treat. C	NON-FASTING Treat. D	NON-FASTING Treat. E	
0.0	0.00 (---)	0.00 (---)	0.00 (---)	0.00
0.5	3.10 (100)	3.68 (108)	2.78 (117)	1.32
1.0	9.33 (31)	8.03 (67)	8.06 (43)	1.00
2.0	10.82 (20)	10.48 (42)	11.45 (28)	0.92
3.0	10.34 (19)	11.39 (21)	12.50 (21)	0.91
4.0	9.96 (20)	11.40 (18)	12.11 (17)	0.94
6.0	9.60 (20)	10.08 (19)	11.19 (17)	0.90
8.0	9.65 (22)	9.24 (24)	10.09 (20)	0.92
12.0	8.15 (28)	7.42 (28)	8.35 (26)	0.89
16.0	6.39 (30)	5.68 (37)	6.22 (29)	0.91
24.0	3.99 (39)	3.58 (55)	3.73 (34)	0.96
36.0	2.37 (45)	1.85 (47)	2.54 (50)	0.73
48.0	1.07 (65)	0.91 (70)	0.97 (69)	0.94
72.0	0.14 (187)	0.13 (216)	0.12 (227)	1.08

TABLE 16

A SUMMARY OF METHAMPHETAMINE PHARMACOKINETIC PARAMETERS FOR 17 SUBJECTS (Non-Fasting)

Parameters	Lemmon's Selegiline Mean (CV%)		Somerset's Eldepryl Mean (CV%)	T/R (D/E)
	Fasting Treat. C	Non-Fasting D	Non-Fasting E	
AUC_{0-72} ng.hr/mL	245.7 (29)	227.3 (32)	252.7 (27)	0.90
AUC_{inf} ng.hr/mL	259.6 (28)	240.1 (31)	266.5 (26)	0.90
C_{max} ng/mL	11.8 (19)	13.1 (20)	13.3 (17)	0.98
T_{max} hours	3.6 (86)	2.8 (42)	3.5 (55)	0.80
$t_{1/2}$ hours	12.4 (21)	11.7 (20)	11.9 (19)	0.98
K_{el} 1/hr	0.058 (19)	0.061 (17)	0.060 (18)	1.01
Ln AUC_{0-72} ng.hr/mL	236.2 (30)	217.7 (30)	244.4 (27)	0.89
Ln AUC_{inf} ng.hr/mL	250.0 (32)	230.3 (30)	258.2 (26)	0.89
Ln C_{max} ng/mL	11.6 (18)	12.8 (21)	13.1 (18)	0.98

Selegiline

Fasting-Non-Fasting Comparison (Treatment C vs D) Lemmon:

The ratios of means for untransformed parameters were 0.54 and 0.48 for AUC0-t and AUCinf respectively and for Cmax the ratio was 0.82. Mean Tmax was 39% more after the administration of food.

Non-Fasting Comparison (Treatment D vs E) Lemmon vs Somerset

The ratios for untransformed parameters were 0.94, 0.93, and 1.05 for AUCo-t, AUCinf and Cmax, respectively. Mean Tmax values were 1.043 and 0.910 for Lemmon (D) and Somerset (E) products after food

administration. The ratios for Kel and t1/2 were 1.28 and 0.78 respectively.The ratios for log-transformed for AUCo-t, AUCinf and Cmax were 0.90, 0.86 and 0.91 respectively.

Desmethylselegiline

Fasting-Non-Fasting Comparison (Treatment C vs D) Lemmon:

The ratio of means for untransformed parameters were 0.94 and 0.94 for AUCo-t and AUCinf respectively and for Cmax the ratio was 1.39. Mean Tmax was 37% more after food administration.

Non-Fasting Comparison (Treatment D vs E) Lemmon vs Somerset:

The ratios for untransformed parameters were 0.97, 0.97 and 0.98 for AUCo-t, AUCinf and Cmax respectively. Mean Tmax values were 1.362 and 1.381 for Lemmon (Treatment D) and Somerset (Treatment E) products after food administration. The ratios for Kel and t1/2 values were 1.00 and 1.01 respectively. The ratios for log-transformed for AUCo-t, AUCinf, and Cmax were 0.94, 0.95 and 0.96 respectively.

Amphetamine

Fasting-Non-Fasting Comparison (Treatment C vs D) Lemmon:

The ratio of means for untransformed parameters were 1.05 and 1.06 for AUCo-t and AUCinf and for Cmax the ratio was 0.90. Mean Tmax was 40.7% less after food administration.

Non-Fasting Comparison (Treatment D vs E) Lemmon vs Somerset

The ratios for untransformed parameters were 0.93, 0.93 and 1.00 for AUCo-t, AUCinf and Cmax respectively. Mean Tmax values were 5.9 and 5.9 for Lemmon (Treatment D) and Somerset (Treatment E) products respectively after food administration. The Kel and t1/2 values differ by 2.17% and 2.55%. The ratios for log-transformed for AUCo-t, AUCinf and Cmax were 1.04, 1.04 and 1.00 respectively.

Methamphetamine

Fasting-Non-Fasting Comparison (Treatment C vs D) Lemmon:

The ratio of means for untransformed parameters were 1.08 and 1.08 for AUCo-t and AUCinf respectively and for Cmax the ratio was 0.90. Mean Tmax was 28.6% less after food administration.

Non-Fasting Comparison (Treatment D vs E) Lemmon vs Somerset

The ratios of untransformed parameters were 0.90, 0.90 and 0.98 for AUCo-t, AUCinf and Cmax respectively. Mean Tmax values were 2.8 and

3.5 for Lemmon Treatment D) and Somerset Treatment E) products respectively after food administration. The Kel and t1/2 values differ by 1.67% and 1.68%. The ratios for log-transformed for AUCo-t, AUCinf and Cmax were 0.89, 0.89 and 0.98 respectively.

Of the 18 healthy adult male volunteers enrolled in the study, one did not complete the crossover. Subject # 18 elected to withdraw from the study for personal reasons prior to Period 2 dosing. Thus a total of 17 subjects completed the study.

There were no serious adverse effects reported during the study.

On the basis of fasting and non-fasting in vivo bioavailability data it is determined that Lemmon's selegiline hydrochloride 5 mg tablets and Somerset's Eldepryl 5 mg tablets are bioequivalent.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 500 mL of purified water at 37°C using USP XXIII apparatus 1 (Basket) at 50 rpm. Results are presented in Table 17. Both the test and reference products meet the dissolution specifications of not less than 80% of the labeled amount of the drug dissolved from the tablet in 20 minutes.

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

FASTING

- Of the 32 healthy adult male volunteers enrolled in the study, 2 did not complete the crossover. Subject # 10 and 31 were withdrawn from the study prior to Period 2 dosing due to medical events related to something other than the study drugs or procedures. Statistical and pharmacokinetic analyses were performed on data from 30 subjects.

TREATMENT A AND B

Selegiline

The ratios of means (with 90% confidence intervals) for the ln-transformed parameters AUCo-t, AUCinf and Cmax were .96 (80-115%), .99 (91-124%) and .99 (80-124%), respectively. For the untransformed data the ratios of arithmetic means were 1.09 for AUCo-t, 1.06% for AUCinf and 1.19 for Cmax. The 90% confidence

intervals were 73 to 144 for AUCo-t, 76 to 139 for AUCinf and 83 to 155 for Cmax. The mean Tmax for the Lemmon product was 0.666 hours, compared with 0.660 hours for the Sumerset product.

Desmethylselegiline

The ratios of means (with 90% confidence intervals) for the ln-transformed parameters AUCo-t, AUCinf, and Cmax were 1.02 (96-107), 1.02(96-107) and 1.03 (97-112) respectively. Similar results were obtained for the untransformed data. The ratios of arithmetic means were 1.03 for AUCo-t, 1.03 for AUCinf and 1.05 for Cmax. The 90% confidence intervals were 97 to 108 for AUCo-t, 98 to 108 for AUCinf and 95 to 114 for Cmax. The mean Tmax for the Lemmon product was 0.846 hours, compared with 0.815 hours for the Sumerset product.

Amphetamine

The ratios of means (with 90% confidence intervals) for the ln-transformed parameters AUCo-t, AUCinf and Cmax were 0.99 (94-105), 0.97(94-104) and 1.00 (96-105), respectively. Similar results were obtained for the untransformed parameters. The ratios of arithmetic means were 1.00 for AUCo-t, 0.97 for AUCinf and 1.00 for Cmax. The 90% confidence intervals were 94 to 106 for AUCo-t, 95 to 105 for AUCinf and 95 to 105 for Cmax. The mean Tmax for the Lemmon product was 6.83 hours, compared with 7.67 hours for the sumerset product.

Methamphetamine

The ratios of means (with 90% confidence intervals) for the ln-transformed parameters AUCo-t, AUCinf and Cmax were 0.97 (90-103), 0.95 (89-101), and 0.99 (95-103), respectively. Similar results were obtained for the untransformed parameters. The ratios of arithmetic means were 0.97 for AUCo-t, 0.95 for AUCinf and 0.99 for Cmax. The 90% confidence intervals were 89 to 104 for AUCo-t, 88 to 102 for AUCinf and 95 to 103 for Cmax. The mean Tmax for the Lemmon product was 4.57 hours, compared with 4.37 for the sumerset product.

- The confidence limits for ln-transformed AUCo-t, AUCinf and Cmax are within the range of 80 - 125% for all three metabolites. Selegiline 90% confidence interval for C_{max} was 73 to 144 but the geometeric mean ratio was 1.00 for Cmax, 1.03 for AUCo-t and 1.06 for AUCinf which is in an acceptable range and is acceptable to the Division of Bioequivalence.Three major metabolites meet the bioequivalence criteria.Very little information is available on the pharmacokinetics of this drug in the literature. Because of the rapid conversion of selagiline to its three metabolites, the Division of Bioequivalence feels that the study is acceptable if three metabolites meet the Division criteria of the bioequivalence study and the geometric mean ratios for selegiline

pharmacokinetic parameters were within the range of 0.8 to 1.25. Plasma concentrations of the parent drug have been too low to measure in previous studies in humans, (Heinonen, E.H., Myllyla, V. Sotaniemi, K et al., "Pharmacokinetics and Metabolism of Selegiline", Acta Neurol. Scand. 126, 83-99, 1989), and metabolites have been used as a measure of selegiline's bioavailability.

- The high intrasubject variability observed for selegiline (intrasubject CV% for ln AUCo-t, ln AUCinf, ln Cmax of 131.2%, 115.9% and 133.8% respectively, results in the wide selegiline confidence intervals observed.

- The assay validation studies conducted by the sponsor are acceptable to the Division of Bioequivalence

- No serious side effects were observed.

- The in vitro dissolution testing conducted on both the test and reference products show greater than 80% of the labeled amount of selegiline hydrochloride dissolved in 20 minutes. The sponsor has conducted dissolution according to the specifications of the Division of Bioequivalence.

- The in vivo fasting bioequivalence study and in vitro dissolution testing are acceptable.

NON-FASTING

- Of the 18 subjects enrolled in the study, one subject (#18) withdrawn prior to period 2 dosing for personal reasons. Thus, a total of 17 subjects completed the study.

TREATMENT C, D, & E

Non-Fasting-Fasting Comparison (Treatment C vs D)

Selegiline

Based on the ratios of means for log-transformed selegiline data, the bioavailability of the Lemmon product (AUCinf) increased with co-administration of food. The mean maximum plasma selegiline concentration increased with the administration of food. Results for the untransformed parameters showed similar results for AUCo-t and AUCinf and for Cmax. Mean Tmax under fasting conditions was 0.637 hours verses 1.043 hours under non-fasting conditions.

Desmethylselegiline

Based on the ratios of means for log-transformed desmethylselegiline data, the bioavailability of the Lemmon product

(AUCinf) increased and the mean maximum plasma desmethylselegiline concentration decreased with co-administration of food. Results for the untransformed parameters showed a similar trend. Mean Tmax under fasting conditions was 0.852 hours versus 1.362 hours under non-fasting conditions.

Amphetamine

Based on the ratios of means for log-transformed amphetamine data, the bioavailability of the Lemmon product (AUCinf) decreased with co-administration of food. The mean maximum plasma amphetamine concentration was approximately same. Results for the untransformed parameters showed a similar trend. Mean Tmax under fasting conditions was 8.3 hours versus 5.9 hours under non-fasting conditions.

Methamphetamine

Based on the ratios of means for log-transformed methamphetamine data, the bioavailability of Lemmon product (AUCinf) decreased and the mean maximum plasma methamphetamine concentration increased with co-administration of food. Results for the untransformed parameters showed similar trend. Mean Tmax under fasting conditions was 3.6 hours versus 2.8 hours after non-fasting conditions.

Non-Fasting Comparison (Treatment D (Lemmon) vs E Somerset)

Selegiline

The ratios of means for log-transformed selegiline parameters AUCo-t, AUCinf, and Cmax were 0.90, 0.86 and 0.91, respectively. The ratios of means for the untransformed parameters AUCo-t, AUCinf and Cmax were 0.94, 0.93 and 1.05, respectively. Mean Tmax values for the Lemmon and Somerset products (under non-fasting conditions) were 1.043 and 0.910 hours respectively.

Desmethylselegiline

The ratios of means for log-transformed desmethylselegiline parameters AUCo-t, AUCinf, and Cmax were 0.94, 0.95 and 0.96, respectively. The corresponding ratios for untransformed parameters showed a similar trend. Mean Tmax values for the Lemmon and Somerset products were 1.362 and 1.381 hours, respectively.

Amphetamine

The ratios of means for the log-transformed amphetamine parameters AUCo-t, AUCinf and Cmax were 1.04, 1.04 and 1.00, respectively. The corresponding ratios of untransformed parameters showed a similar

trend. Mean Tmax values for the Lemmon and Somerset products were 5.9 and 5.9 hours, respectively.

Methamphetamine

The ratios of means for the log-transformed methamphetamine parameters AUCo-t, AUCinf and Cmax were 0.89, 0.89 and 0.98, respectively. The corresponding ratios for untransformed parameters showed similar trend. Mean Tmax values for the Lemmon and Somerset products were 2.8 and 3.5 hours, respectively.

- Administration of selegiline with food produced a large increase in its bioavailability (i.e., AUCinf). Based on the selegiline,desmethylselegiline,amphetamine and methamphetamine results, the Lemmon formulation meets the bioequivalence criteria of 0.8-1.2 for the ratios of the means.

- The Lemmon and Somerset selegiline hydrochloride 5 mg tablets, appear to show comparable bioavailability under non-fasting conditions.

- No serious adverse events were recorded during this period.

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting and non-fasting bioequivalence studies conducted by Lemmon Company on its Selegiline Hydrochloride 5 mg tablets, lot # K-18339, comparing it to Eldepryl 5 mg tablets, lot # 3Z022M, manufactured by Somerset has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting and non-fasting conditions the Lemmon's Selegiline Hydrochloride 5 mg tablets are bioequivalent to the reference product, Eldepryl 5 mg tablets, manufactured by Somerset.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of purified water at 37°C using USP XXIII apparatus 1 (basket) at 50 rpm. The test should meet the following specifications:

> Not less than 80% of the labeled amount of the drug in the tablet is dissolved in 20 minutes.

3. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing and the study is acceptable.

Man.M.Kochhar

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramanand M. Mhatre 7/15/96

Concur: _____ Date: 7/17/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/3-1-96; 3-27-96; 7-15-96;74-744 BIO

cc: ANDA # 74-744 original, HFD-630, HFD-600 (Hare), HFD-344 (CViswanathan) HFD-658 (Mhatre, Kochhar), Drug File.

(Please select Typeover for Input.)

Table 17 . In Vitro Dissolution Testing

Drug (Generic Name): Selegiline Hydrochloride
Dose Strength: 5 mg
ANDA No.: 74-744
Firm: Lemmon
Submission Date: September 8, 1995
File Name:

I. Conditions for Dissolution Testing:

USP XXIII Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium: Volume: 500 Purified Water
Specifications: NLT 80% in 20 minutes
Reference Drug: Eldepryl

Assay Methodology: UV

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # K-18339 Strength 5 MG			Reference Product Lot # 3Z022M Strength 5 MG		
	Mean %	Range	RSD	Mean %	Range	RSD
10	97	91 TO 104	4.0	87	78 TO 95	7.5
20	98	95 TO 101	2.0	94	91 TO 100	2.9
30	97	93 TO 105	3.3	93	88 TO 97	3.1

Figure 1

Project No. 941527

Mean Plasma Selegiline Concentrations

(Linear Plot)

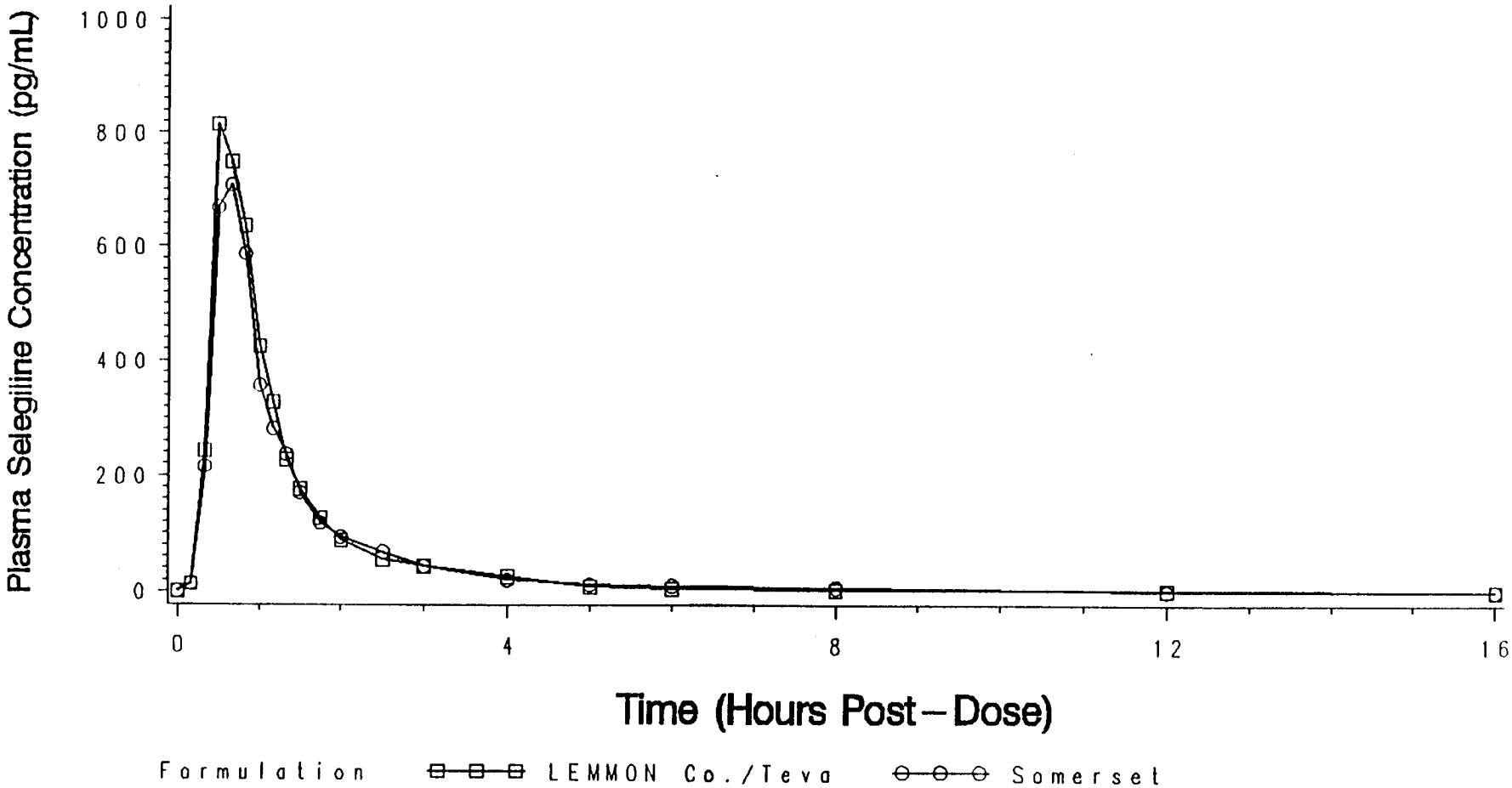


Figure 2.

Project No. 941527

Mean Plasma Desmethylselegiline Concentrations

(Linear Plot)

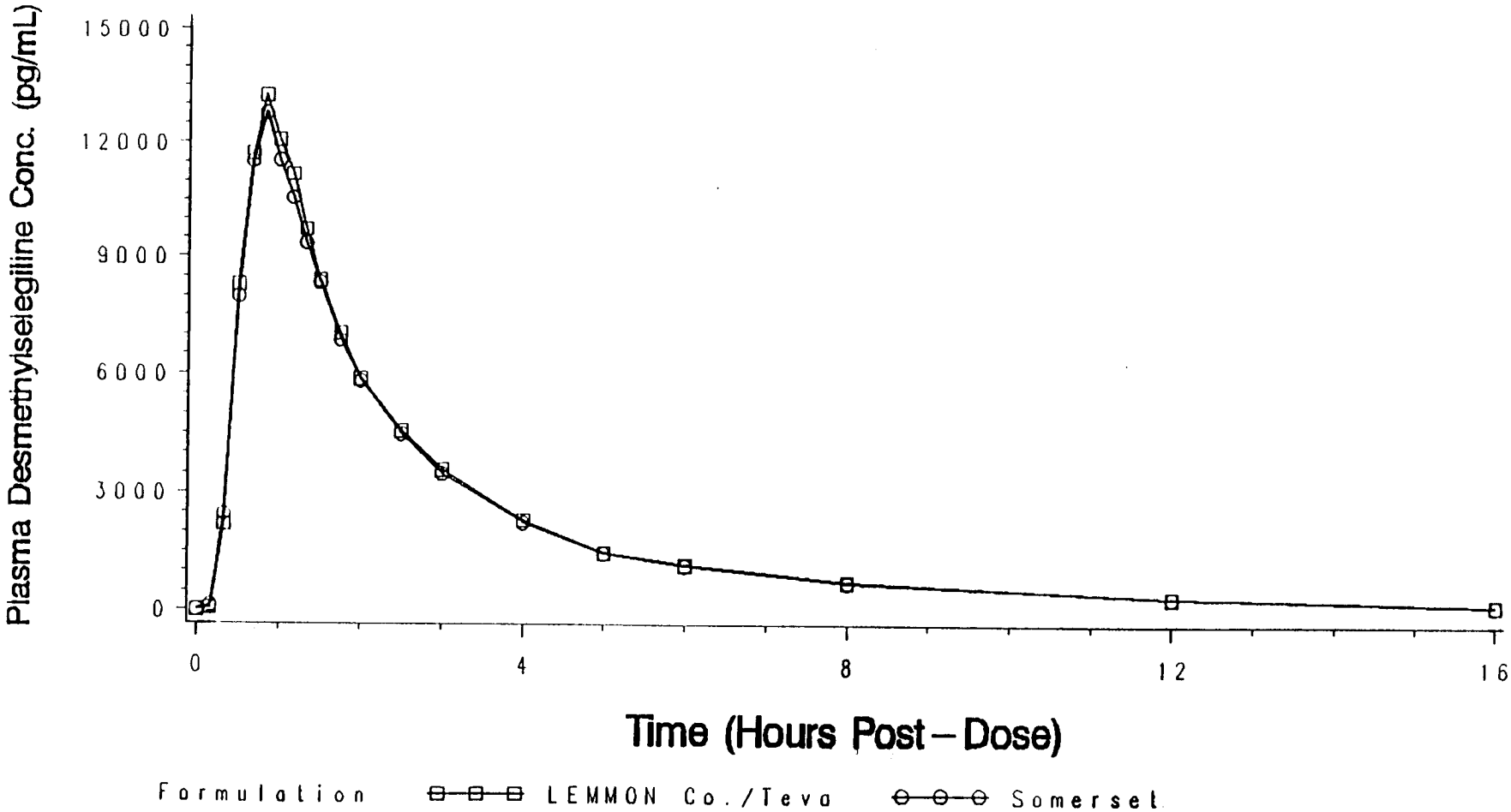


Figure 3

Project No. 941527

Mean Plasma Amphetamine Concentrations

(Linear Plot)

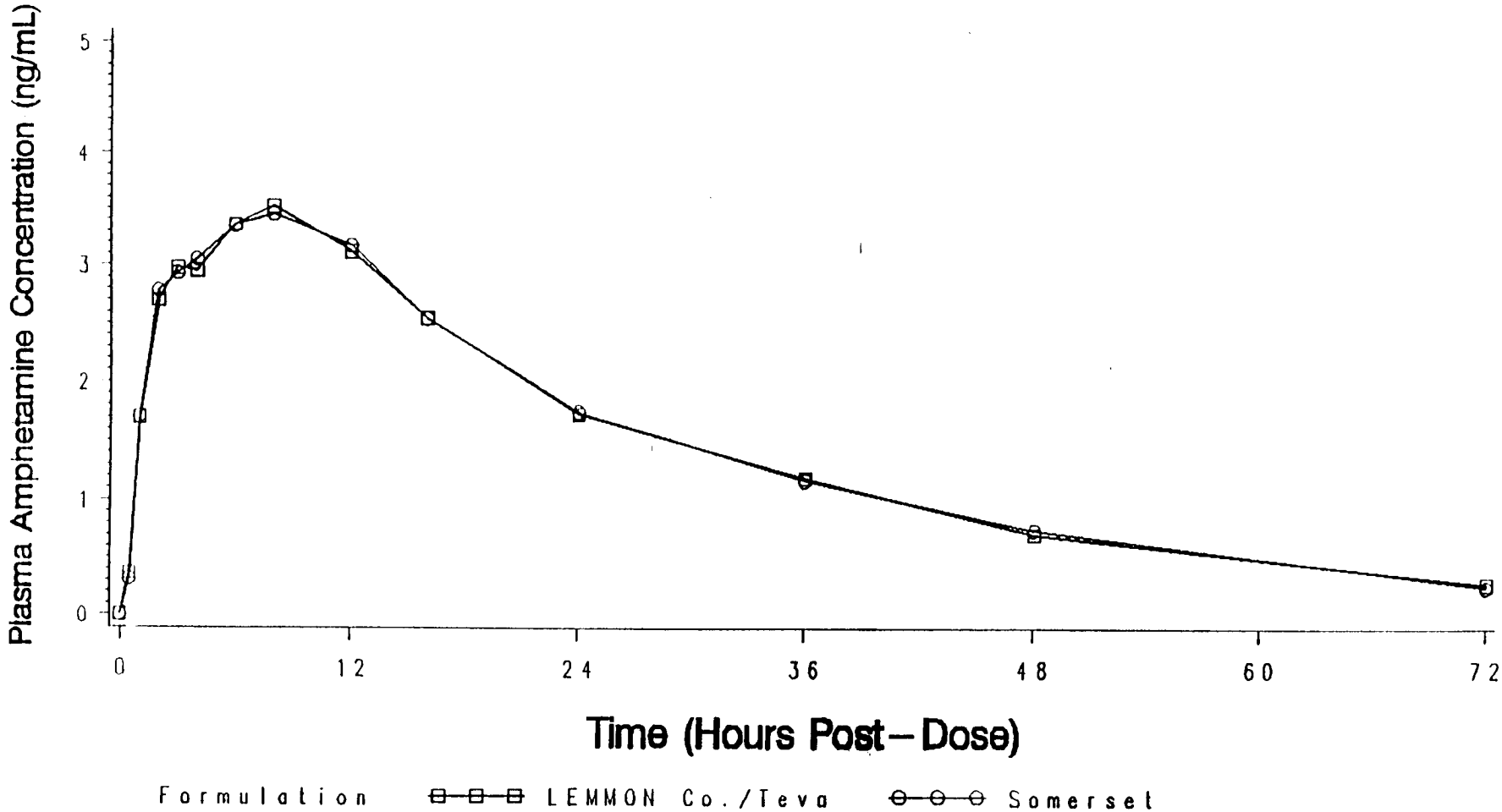


Figure 4

Project No. 941527

Mean Plasma Methamphetamine Concentrations

(Linear Plot)

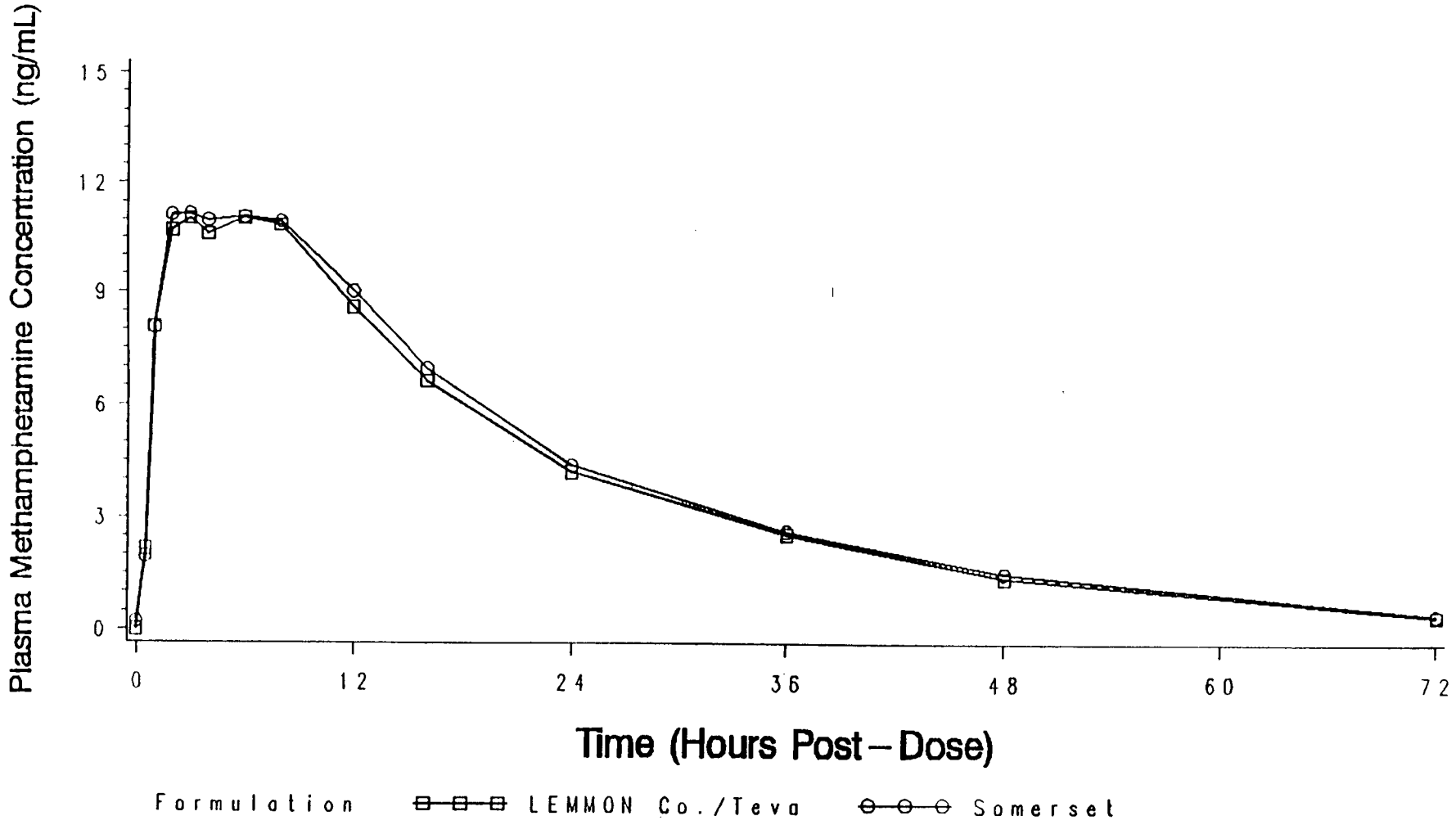


Figure 5

Project No. 941528

Mean Plasma Selegiline Concentrations

(Linear Plot)

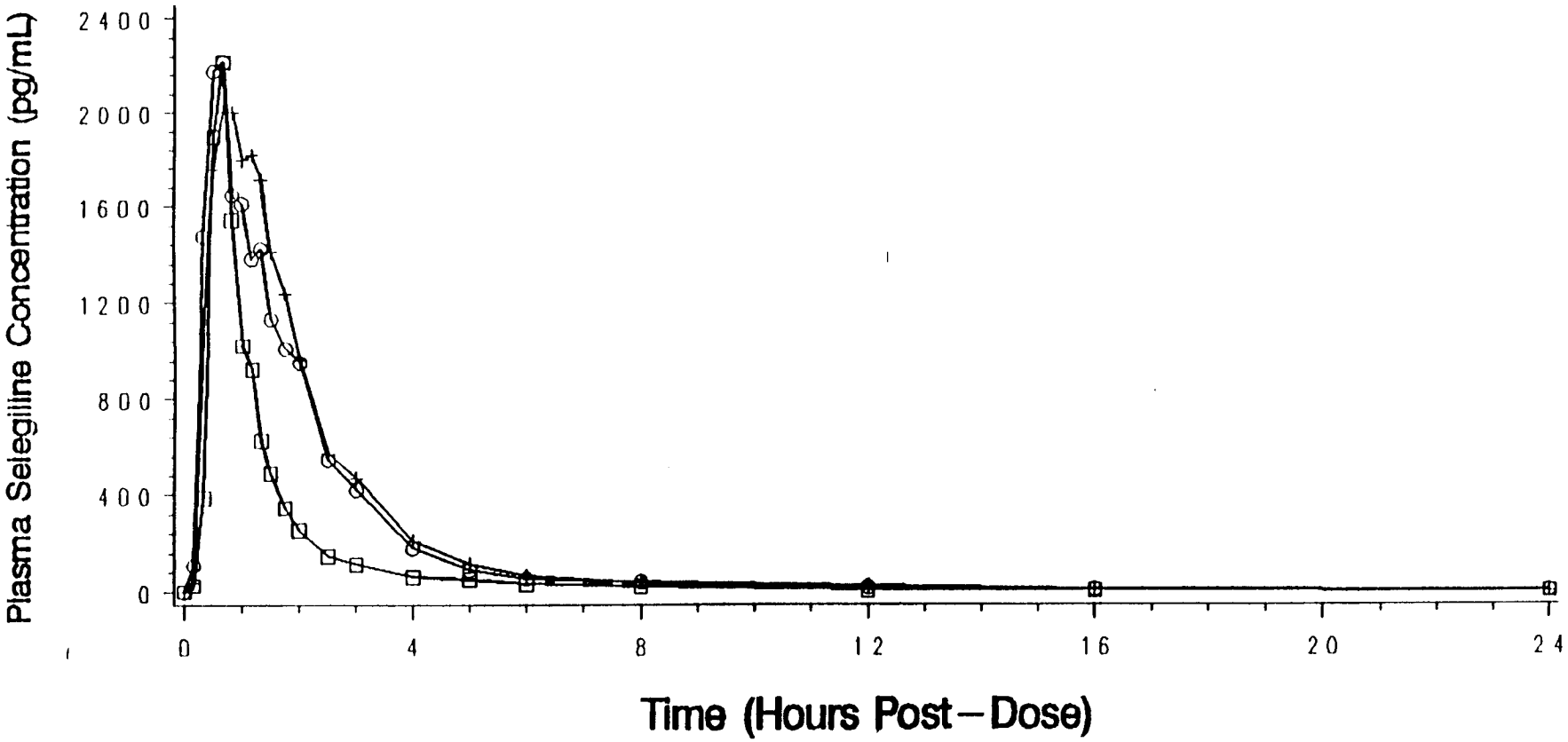


Figure 6

Project No. 941528

Mean Plasma Desmethylselegiline Concentrations

(Linear Plot)

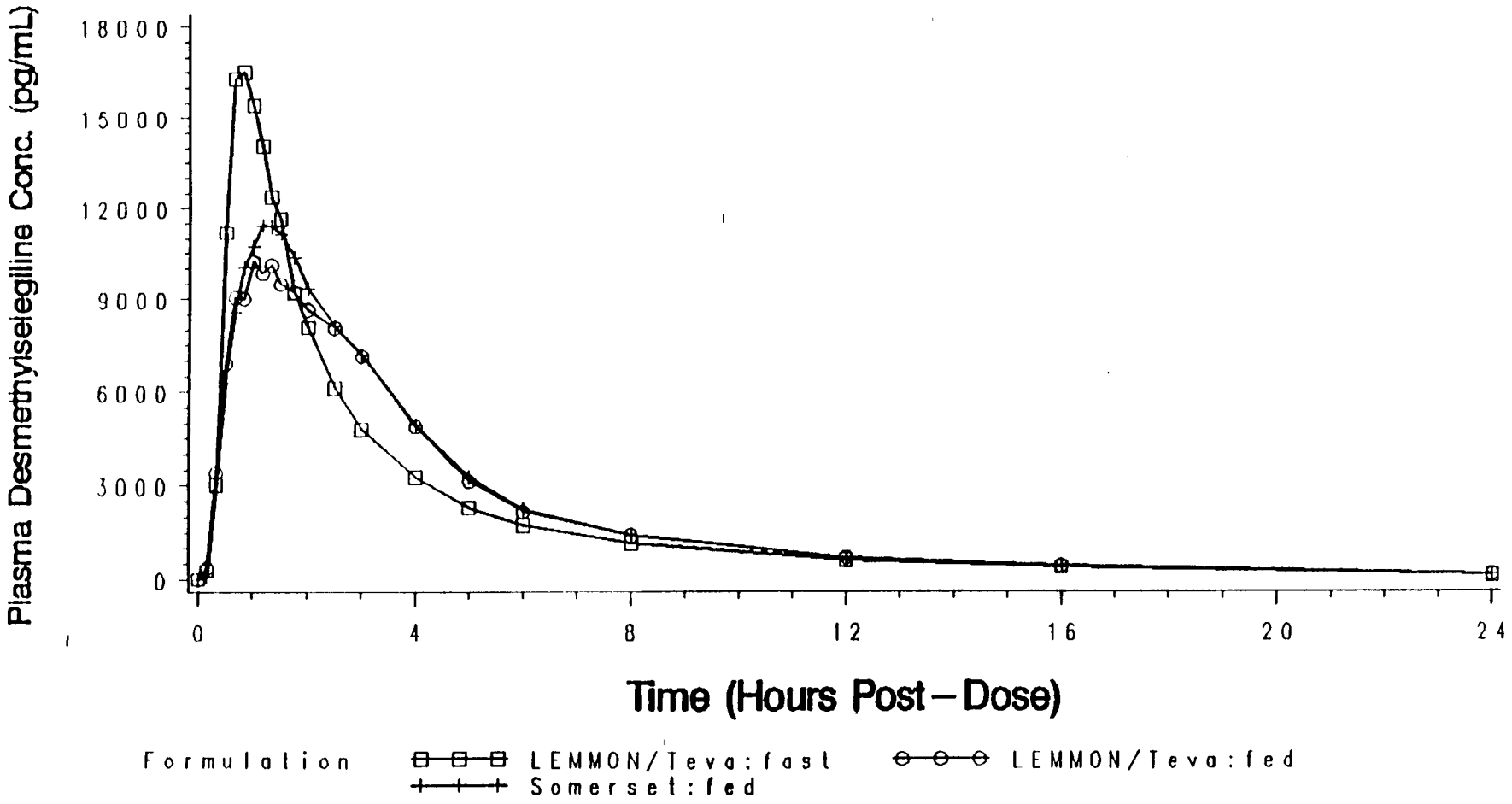
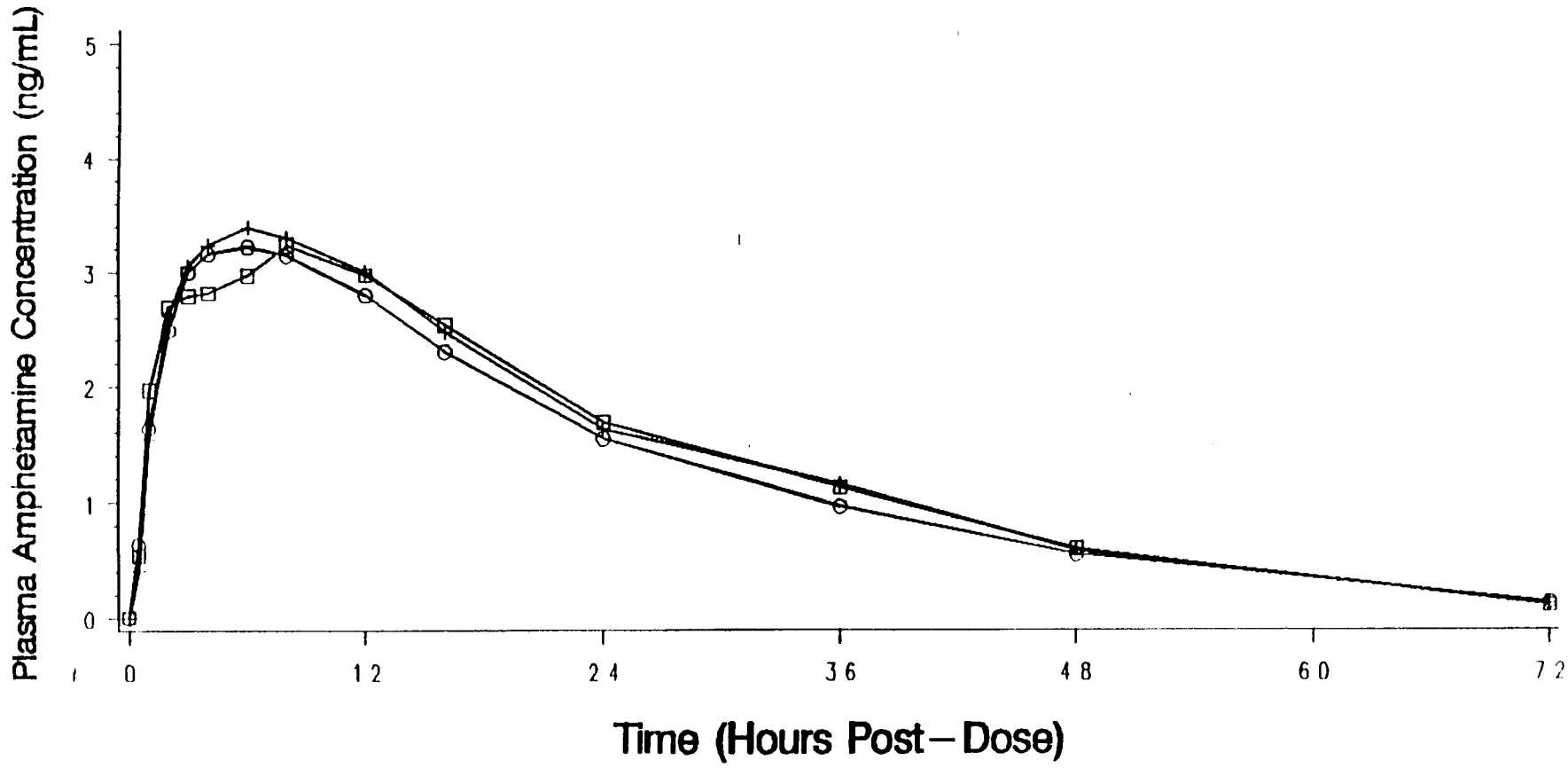


Figure 7

Project No. 941528

Mean Plasma Amphetamine Concentrations

(Linear Plot)



DEFAULT (07MAY95)

Figure 8

Project No. 941528

Mean Plasma Methamphetamine Concentrations

(Linear Plot)